REMARKS

Claim 27 is amended herein to correct an error in form.

Statement of the Substance of the Interview

The courtesy of the Examiner's Interview on January 13, 2010 is noted with appreciation. Applicants are in agreement with the Interview Summary provided with this Office Action. It is understood that it is the position of the Office that the claims are not patentable, and would not be patentable if limited to MP + PP in the range of 0.375 – 1 mg/ml, because the composition would be expected to be anti-microbial as when a third anti-microbial agent is present. It is further understood that it is the position of the Office that the claims are not commensurate in scope with the data.

Applicants respectfully disagree with these positions, as explained below.

Rejection of claims 1-2, 5, 12, 17 and 27 under 35 USC 103

Claims 1-2, 5, 12, and 17 stand rejected as obvious over DeLongueville et al. (WO 02/47689 A2), Gilliland 1 (1992; J. Appl. Bacteriol.; 72: 252-57); and Gilliland 2 (1992; J. Appl. Bacteriol.; 72:258-61) and Doron et al. (2001 Int'l J. Antimicrobial Agents 18: 575-578) in view of Routledge (1998; Toxicol. Appl. Pharmacol.; 153:12-19). This rejection is respectfully traversed.

The present invention is based on the surprising finding that the active substances belonging to the family of substituted piperazines, such as levocetirizine, possess a preservative effect in aqueous solutions (specification, page 2, lines 4-6). Thus, applicants herein have made the unexpected finding that a pharmaceutical composition comprising such an active substance and a reduced amount of preservatives is stable, i.e. resistant to microbial contamination, for a long period of time. (id., lines 11-15) Independent claim 1 is directed to a composition comprising levocetirizine, and a preservative, wherein the preservative is a mixture of methyl parahydroxybenzoate and propyl parahydroxybenzoate in a ratio of 9/1 expressed in weight, said mixture being present in an amount of more than 0 and less than 1.125 mg/ml of the composition.

Applicants submit that it is wholly unexpected that a levocetirizine composition could be made with both a low concentration of parabens and an MP/PP ratio of 9, and still be resistant to microbial contamination. It is noted that pharmaceutical compositions of other drugs using parabens as preservatives use either much higher concentrations of parabens, or much lower ratios of MP/PP, or both, as shown in the following references, submitted herewith with a Supplemental Information Disclosure Statement.

- U.S. 4,705,683 at col. 3, lines 15-25 and col. 3 line 65 – col. 4 line 8, discloses compositions of cimetidine and ranitidine, respectively, having a combined methyl paraben and propyl paraben of 0.172 g/100 ml or 1.72 mg/ml and a MP/PP ratio of 6.8, both outside the presently claimed values.
- U.S. 6,004,968 discloses pharmaceutical composition of lamivudine and parabens. At col. 4, lines 16-26, the reference discloses that for oral solutions and suspensions, the range of methyl paraben concentration may be 0.096%-0.2% (0.96 mg/mL to 2 mg/mL) and the range of propyl paraben concentration may be 0.01% to 0.02% (0.1 to 0.2 mg/mL), but the preferred ranges are 0.15-0.2% (1.5 mg/mL to 2 mg/mL) for methyl paraben and 0.018-0.019% (0.18 mg/mL to 0.19 mg/mL) for propyl paraben, such that the preferred range for combined parabens and preferred valued for MP/PP are both outside the scope of the present claims. The composition of Example 1 (the only composition disclosed in the reference) has total parabens of 1.6 mg/ml, outside the presently claimed range.
- US 2009/0137645 discloses a famotidine composition in which a first granulate comprising famotidine is mixed with a second granulate comprising parabens. The ratio of MP/PP is 5 (Tables 1-4) well outside the presently claimed range.
- As disclosed at http://www.rxlist.com/levo-dromoran-drug.htm, the commercial drug levo-dromoran is sold in 1 ml ampoules containing the drug plus 1.8 mg methyl paraben and 0.2 mg propyl paraben, for a total of 2.0 mg parabens per ml of solution, well beyond the upper limit of 1.125 mg parabens/ml solution recited in the present claims.
- The treatise Remington the Science and Practice of Pharmacy, 21st ed., 2005, pp. 748-749, discloses in Table 39-2 that methyl and propyl parabens are each

typically used in concentrations of 0.1-0.25 w/w%; when combined, these would yield a minimum concentration of 0.2% total parabens, or 2 mg/mL, well beyond the presently claimed range. The table also suggests that the maximum MP/PP ratio would be 2.5, well below the value of 9 recited in the present claims. The use of parabens generally as antimicrobial agents is discussed generally at page 749, left column, under "Esters."

From the foregoing, it may be seen that those skilled in the pharmaceutical arts would not have been led to expect that a liquid pharmaceutical composition comprising levocetirizine could be prepared with a total parabens concentration of no more than 1.125 mg parabens/ml of solution and a methyl paraben to propyl paraben ratio of 9:1, to achieve a composition with the anti-microbial properties required of a pharmaceutical composition. One skilled in the art would have been led to believe that either the overall quantity of parabens would have to be much higher, or the ratio of methyl paraben to propyl paraben would have to be much lower, or both. The quantitative limitations of claim 1 render that claim, and all claims dependent thereon either directly or indirectly, non-obvious over the art of record in this case.

The arguments and remarks set forth in the Response filed October 23, 2009 are incorporated herein by reference.

The present Action restates the rejection from the prior action, then states at page 8: "It is noted that the arguments provided on the record were considered to be persuasive. However, the combination that includes the Doron reference is considered to render the instant claims obvious over the references in combination." The Action notes that Fig. 1 of Doron includes a data point with 0.015 w/v MP, corresponding to MP + PP of 0.45 mg/ml.

This data point does not render the claimed invention obvious for at least four reasons:

- Doron does not relate to the use of parabens as an anti-bacterial preservative for another drug in a pharmaceutical composition. Doron does not teach the use of parabens in combination with any other pharmaceutical. Therefore, one cannot predict from Doron what effect parabens would have when used in combination

with any other pharmaceutical product, or what concentration or ratios of parabens would be effective.

- The data in Fig. 1 of Doron relied on in the Action is the antibacterial effect on **immobilized** *S. sobrinus*. And as the applicants noted in their response to the Office Action mailed February 25, 2009, Doron expressly states that there is a stronger antibacterial effect of a combination of parabens on immobilized bacteria compared to planktonic bacteria. *See* Doron, p. 578, first paragraph, which also states that the effects of individual parabens is similar against planktonic bacteria and immobilized bacteria.

  At least two points follow from this. First, the difference in antibacterial effects of individual parabens versus combinations of parabens against immobilized and planktonic bacteria demonstrate a degree of unpredictability in extrapolating the antibacterial data to new situations.

  Second and moreover, because combinations of parabens are more effective against immobilized bacteria than planktonic bacteria, **the results reported by Doron in Fig. 1 for immobilized bacteria cannot be extrapolated to what one of ordinary skill in the art would expect in a liquid composition as presently claimed (*i.e.* against planktonic bacteria).**

- The ratio of methyl paraben to propyl paraben at the selected data point is 0.5/1, far removed from the 9/1 ratio recited in the present claims. In fact, all the samples in Figs. 1 and 2 of Doron have MP/PP ratios of 0, 0.5, 1, and 2. Nothing in the reference suggests even trying a 9/1 MP/PP ratio, much less that such a ratio would be effective.
- Fig. 1 of Doron shows that at the selected data point the viable bacteria count is greater than 35%, far greater than what would be acceptable for a pharmaceutical product; therefore Doron teaches that 0.45mg/ml is not an effective antimicrobial agent. As the applicants stated in their response to the Office Action mailed February 25, 2009,

  > While, as the Office noted, Doron teaches that combinations of parabens have a synergistic effect on planktonic bacteria, in the very same sentence

> Doron states, "although a complete antibacterial effect is not always achieved." The significance of this statement cannot be over-emphasized because to be safe, useful, and achieve regulatory approval, **a complete antibacterial effect must be achieved**. Furthermore, the antibacterial efficacy of a pharmaceutical composition must be continuously maintained over long periods of time and multiple potential exposures to bacteria. While liquid pharmaceutical formulations are manufactured to be bacteria-free and sealed, they may be repeatedly exposed to the risk of bacterial contamination each time the container is opened (such as with drops). An acceptable pharmaceutical formulation must be completely bacterial resistant under such circumstances throughout the life of the product.

Fig. 1 of Doron shows that the only way to achieve complete eradication of bacteria, as would be required for a pharmaceutical agent, is with methyl paraben of 0.125 w/v% combined with 0.03 w/v% propyl paraben, for a total parabens of 0.155 w/v% or 1.55 mg/ml. Thus Doron teaches that to achieve complete eradication of bacteria both the MP/PP ratio and the total MP + PP content must be well outside scope of the present claims.

- Doron is evaluating various combinations of parabens to serve as antibacterial agents in the oral cavity, which is far different use from serving as a pharmaceutical preservative in a liquid composition, as presently claimed.

The fact that the selected data point "indicates that some reduction in viable bacteria would be expected even at low amounts" does not render the claimed invention obvious, because "some" reduction in bacteria is not the standard for a pharmaceutical composition. The goal for a pharmaceutical composition is substantially complete eradication of bacteria, to protect the pharmaceutical composition from bacterial contamination. The Action provides no scientific basis or reasoning why altering the MP/PP ratio of Doron to that recited in the present claims would be expected to yield a complete antibacterial result. Indeed, Doron suggests to the contrary when it notes that while individual parabens are equally effective against immobilized and planktonic bacteria combinations of parabens are more effective against immobilized bacteria than planktonic bacteria. This suggests that altering the ratio of parabens (at least down to 0) changes the antibacterial effect. One of ordinary skill in the art cannot predict the results of altering the ratio of parabens based on the cited art, so, contrary to the assertions in the Action, the ratio in Doron does not and cannot render a ratio of 9/1 obvious.

One skilled in the art reading Doron would have no reason to recognize that the presence of levocetirizine in the claimed composition unexpectedly allows for the use of a lower concentration of parabens when the parabens are used in the claimed ratio while still achieving essentially complete eradication of bacteria, as recognized by Applicants herein.

To the extent the Action notes at page 9 that a third active agent would result in further killing at the lower paraben concentrations, the applicants respectfully submit that this is irrelevant because it does not detract from the fact that the particular combination of parabens in the recited amounts and ratio surprisingly has an completely antibacterial effect. Because the combination of parabens in the recited amounts and ratio possess an unexpected property (*i.e.* effective antibacterial action when used in combination with levocetirizine), the claimed combination of parabens with levocetirizine must be non-obvious and any composition containing it must be non-obvious too. The optional presence of additional components does not detract from this.

In response to the three points raised on page 10 of the Action:

1) to the extent that Doron is not a direct comparison and therefore a cutoff point from Doron cannot be applied to show that the present results are unexpected, then the fact that it is not a direct comparison also means that the data cannot be used to show that the present results are expected;

2) the possible effects of MP and PP with a third agent are irrelevant because, as noted above, whether a third agent would lead to further antibacterial activity does not detract from the fact that the particular combination of parabens in the recited ratio and amounts has an unexpected antibacterial effect;

3) the unexpected results are shown in the specification at Example 4, pages 12 – 14. The fact that other additional ingredients as set forth in Table 2 are present does not mean that the data is not commensurate in scope with the claims. Table 4 shows the formulations of two compositions, an oral solution and drops. The drops contain a concentration of levocetirizine ten-fold greater than the oral solution. As shown in a comparison of Tables 5 and 6, the drops composition had a significantly greater anti-microbial effect than the oral solution composition with respect to Candida albicans and Aspergillus niger, demonstrating the unexpected antibacterial effect of levocetirizine with respect

to these two innocula. The results shown in these two tables then can be compared with the results shown in Tables 15-20. These show results for "oral solutions ad drops containing levocetirizine according to example 2 but also containing mixtures of" parabens. With all the same ingredients, but with the addition of the recited amount of parabens in a 9:1 ration of MP/PP, these compositions showed superior antimicrobial activity, even with respect to Candida albicans and Aspergillus niger. Thus it is the presence of the parabens in the recited ratio and amounts in combination with levocetirizine that provides the unexpected antimicrobial properties. The other ingredients, present in Example 2 and Example 4, were not responsible for the results achieved in Example 4.

As to Routledge's incentive to use lower levels of parabens due to their estrogenic activity; that incentive fails where such lower levels are shown in Doron to be ineffective. If anything, Routledge demonstrates a long-felt need for a pharmaceutical composition that could achieve substantially complete eradication of bacteria while minimizing the estrogenic effect of the preservatives in the composition. It was heretofore unrecognized that such a need could be met by using such a small quantity of parabens at the 9:1 MP/PP ratio in a levocetirizine composition as presently claimed.

In view of the foregoing, the applicants respectfully request reconsideration and withdrawal of this obviousness rejection.

If there are any questions or comments regarding this application, the Examiner is encouraged to contact the undersigned in order to expedite prosecution.

Respectfully submitted,

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